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14 UNITED STATES DISTRICT COURT
15 SOUTHERN DISTRICT OF CALIFORNIA
16

17 GEN-PROBE, INCORPORATED,

18 Plaintiff,

19 v.

20 VYSIS, INC.,

21 Defendant.
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CASE NO. 99CV 2668H (AJB)

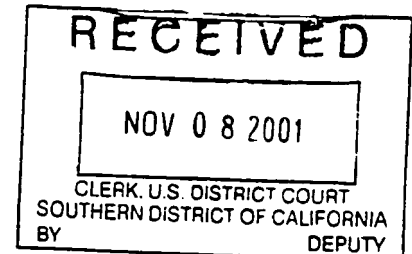
**VYSIS' SUPPLEMENTAL
OPPOSITION TO GEN-PROBE'S
MOTION FOR PARTIAL SUMMARY
JUDGMENT OF
NONINFRINGEMENT UNDER THE
DOCTRINE OF EQUIVALENTS**

Date: November 19, 2001

Time: 10:30 a.m.

Place: Courtroom 1

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25 Pursuant to the Court's November 2, 2001 Order, Vysis hereby submits its Supplemental
26 Opposition to Gen-Probe's Motion for Partial Summary Judgment of Noninfringement Under the
27 Doctrine of Equivalents.
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I. INTRODUCTION

Through the deposition of Gen-Probe’s expert witness, Nobel laureate Dr. Kary B. Mullis, Vysis has unearthed a wealth of new evidence that bears on the application of the legal doctrine of equivalents at issue in this motion and also the Court’s earlier construction of the claims of the ‘338 patent. That evidence further demonstrates that critical facts underlying Gen-Probe’s motion for summary judgment of noninfringement under the doctrine of equivalents are incorrect and sharply disputed. But far more significantly, that newly-discovered evidence shows that Dr. Mullis, one of the world’s renowned experts on nucleic acid amplification, viewed the claims of the ‘338 patent as encompassing *specific in vitro amplification* techniques – such as PCR. Dr. Mullis’s own understanding of the claims of the ‘338 patent confirms what everyone associated with the ‘338 patent – the patent owner, the inventors, the PTO, and even Gen-Probe – has understood: that the claims of the ‘338 patent encompass specific amplification techniques. Accordingly, for the reasons more fully set forth herein, the Court should deny Gen-Probe’s motion and reconsider its previous construction of the claims of the ‘338 patent.

II. NEW EVIDENCE FROM DR. MULLIS DEMONSTRATES WHY THE COURT’S CLAIM CONSTRUCTION IS INCORRECT

A. Dr. Mullis Viewed the Claims as Encompassing Specific Amplification Techniques

Dr. Mullis’s Declaration asserts that specific amplification methods are excluded from the ‘338 patent. (Mullis Decl., ¶¶ 46-47.)¹ Yet at his deposition, Dr. Mullis produced a document clearly showing that he views the term “amplifying” as used in the claims of the ‘338 patent to encompass specific amplification techniques such as PCR. That document, attached as Exhibit (“Ex.”) A, was drafted by Dr. Mullis on January 23, 2001. In that document, Dr. Mullis states that **“People were and still are snatching mRNAs out of extracts with oligo-dT-cellulose every day,**

¹ Unless otherwise indicated, Vysis will use the same abbreviation conventions in this Supplemental Opposition as used by Gen-Probe in its opening Memorandum and by Vysis in its Opposition. All references to Exhibits refer to exhibits attached to the accompanying Supplemental Declaration of L. Scott Burwell.

1 eluting them, and then doing RT-PCR on them.”² (Ex. A at 1 (emphasis in original).) Dr. Mullis
2 further stated:

3 **I think this fairly common process reads directly on Claim 1, A, B,
4 and C!!. Also claims 2-5, 7-11, and all their derivatives.**

5 (*Id.* (emphasis in original), see also Mullis Dep., Ex. B, at 125-28.) Dr. Mullis confirmed his view
6 that practicing target capture followed by specific amplification would infringe the claims of the
7 ‘338 patent on the next page:

8 **I think I would be infringing claim 20 if I were to provide a kit to:**

- 9 (a) Purify DNA from a tube of blood . . .
10 (b) Amplify with PCR . . .
11 (c) Put the amplified target on a membrane . . . and
12 (d) Probe with a labeled oligo

13 (Ex. A at 2 (emphasis in original).)

14 Clearly, upon reading the specification and claims of the ‘338 patent, Dr. Mullis viewed the
15 term “amplifying” as used in those claims as encompassing *specific* amplification techniques, such
16 as PCR. Had he understood the claims to be limited to non-specific amplification techniques, he
17 could not have thought that the use of PCR amplification techniques would infringe the ‘338 patent.³
18 Dr. Mullis’s own untutored understanding of the term “amplifying” demonstrates that the Court’s
19 June 20, 2001 claim construction is incorrect. Anyone skilled in the art reading the specification and
20 claims of the ‘338 patent would immediately understand that the term “amplifying” included specific
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24 ² “RT-PCR” is a specific amplification technique in which the PCR process is preceded by
25 the creation of double-stranded DNA from RNA using reverse transcriptase (RT). (See Transcript of
26 Deposition of Dr. Kary B. Mullis (“Mullis Dep.”), Ex. B, at 126-27.)

27 ³ Dr. Mullis reached his opinion fully cognizant that the examples of the ‘338 patent focused
28 on non-specific amplification, acknowledging that “some variant of this method could have
obviously been employed prior to a *specific* nucleic acid amplification such as [PCR].” (Ex. A
(emphasis added).) Only *after* Gen-Probe’s in-house lawyer told Dr. Mullis what Gen-Probe needed
to prove to win its motion for summary judgment of noninfringement did he consider the claims of
the ‘338 patent might be limited to non-specific amplification. (Mullis Dep., Ex. B, at 129-31.)

1 amplification techniques, such as PCR.⁴ Nobel laureate Kary Mullis understood that term as such
2 and so did the inventors, the patent owner, and the PTO. (Vysis' Opposition Memorandum at 10-
3 16.) Vysis invites the Court to do the same, and correct its earlier, flawed claim construction ruling.⁵

4 **B. Dr. Mullis Views the Specification of the '338 Patent as Explicitly**
5 **Referring to Amplification Using a Specific Primer**

6 Dr. Mullis's testimony also contradicts the Court's conclusion with respect to the disclosure
7 of Example 5 of the '338 patent. That Example discloses an alternative method to using random
8 oligohexamer primers, in which "the double stranded DNA can be formed by synthesis starting from
9 capture probe a." ('338 patent, col. 31, lines 48-49.) In the process, the capture probe acts as the
10 primer. Since the capture probe binds specifically to the target DNA, the capture probe is a specific
11 primer to the target. Vysis contended that this alternative method was an example of specific
12 amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the
13 target organism. (See May 25, 2001 Persing Decl., ¶ 13.) The Court disagreed. (June 20, 2001
14 Order at 6-7.)

15 Dr. Mullis has now confirmed that the alternative technique of Example 5 is an example of
16 specific amplification. Dr. Mullis testified that "capture probe a" is a specific primer (Mullis Dep.,
17 Ex. B, at 101) and that use of "capture probe a" as the primer would lead to "a more specific
18 amplification." (Mullis Dep., Ex. B, at 101-03.) This testimony is further reason for the Court to
19 reconsider its earlier claim construction ruling.

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22 ⁴ Indeed, PCR was extraordinarily well-known by the filing date of the '338 patent. By
23 December 1987, there were at least a thousand published papers on PCR. (Mullis Dep., Ex. B, at
24 50.) It was the most commonly used in vitro amplification technique known in the art. (Mullis
25 Dep., Ex. B, at 51.)

26 ⁵ Dr. Mullis also provided testimony disagreeing with the Court's opinion that "the ['338]
27 prosecution history indicates that the idea of amplification by first using specific target capture
28 techniques is close enough to the goals of PCR to be 'obvious' to the PTO in light of the Mullis
patents." (June 20, 2001 Order at 9.) To the contrary, Dr. Mullis testified that it would not have
been obvious in 1987 to substitute nonspecific amplification techniques for PCR. (Mullis Dep., Ex.
B, at 124-25.) Clearly the PTO's rejection of the Collins application over the Mullis patents must
have been because the claims *encompassed* PCR, and not because target capture combined with non-
specific amplification was obvious in view of PCR.

1 **C. Dr. Mullis Confirms that the Permissive Language Used in the '338**
2 **Specification Does Not Limit the Claimed Invention**

3 The Court found the disclosure of the '338 patent to be limited to use of non-specific
4 amplification primers because the specification stated that such non-specific techniques "can" be
5 used and that specific primers were not "needed." Dr. Mullis's own patents and publications show
6 that permissive language describing an invention, such as that used in the specification of the '338
7 patent, cannot be read to *limit* the invention. For example, in a publication on PCR in the journal
8 *Methods in Enzymology*, Dr. Mullis stated that "It is *not necessary* that the sequence to be
9 synthesized enzymatically be present initially in a pure form; it *can* be a minor fraction of a complex
10 mixture, such as a segment of a single-copy gene in whole human DNA." (Ex. C (emphasis added).)
11 Dr. Mullis confirmed that that language merely demonstrated a benefit of PCR, but was not intended
12 to limit the use of PCR to unpurified DNA:

13 A: . . . To say that it can be, it says it is not necessary that the
14 sequence to be synthesized enzymatically be present initially in a pure
15 form. It's not. *It doesn't mean you can't start with something in a pure*
16 *form.* In fact, you can start with something that has been amplified
17 already, and it's just one fragment.

18 Q: So the ability to start with DNA that was not in pure form was a
19 benefit of PCR but not a limitation on the application of its use?

20 A: Right.

21 (Mullis Dep., Ex. B, at 54 (emphasis added).) Dr. Mullis testified that similar language in another
22 publication (Ex. D), describing PCR as "eliminating the need" for certain steps, did not limit the
23 described invention. (Mullis Dep., Ex. B, at 69.)

24 Further, Dr. Mullis testified that he expected that his own PCR patent would *not* be limited to
25 just the examples described in the patent. (Mullis Dep., Ex. B, at 63-65.) Indeed, notwithstanding
26 the statement in his patent that the PCR process "obviates the need for extensive purification of the
27 product," Dr. Mullis contended that his patent covered the use of PCR even when a purification step
28 was involved. (Ex. E; Mullis Dep., Ex. B, at 65.)

 Dr. Mullis's testimony unambiguously confirms that language referring to techniques as
 "not necessary" or "eliminating the need" for those techniques merely serves to highlight *benefits* of
 an invention, and does not *limit* the invention as excluding the "unnecessary" techniques. A

1 different standard cannot apply to the permissive language of the '338 patent, in which specially
2 tailored primers are merely described as not needed. ('338 patent, col. 30, lines 30-40.) Certainly,
3 as demonstrated by Dr. Mullis's testimony, the '338 specification does not *limit* the claimed
4 invention to only non-specific amplification techniques.

5 **III. DR. MULLIS'S TESTIMONY CONFIRMS THE EQUIVALENCE BETWEEN**
6 **TMA AND THE AMPLIFICATION TECHNIQUES OF THE '338 PATENT**

7 **A. Dr. Mullis Admits that He Did Not Consider the Context of the Invention**
8 **of the '338 Patent**

9 As discussed in Vysis' Opposition memorandum, Gen-Probe's motion relies upon broad,
10 generalized assertions concerning differences between specific and non-specific amplification
11 techniques. Those assertions, supported solely by the Declaration of Dr. Mullis, are made in a
12 vacuum. They do not perform the relevant analysis under the doctrine of equivalents: whether, *in*
13 *the context of the claimed invention*, the substitute element plays a role substantially different from
14 the claimed element. See *Warner-Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17, 40 (1997).

15 Dr. Mullis admitted at his deposition that his function-way-result analysis only addressed
16 *generalized* differences between specific and non-specific amplification and not the claimed
17 invention as required by the law:

18 Q: I mean, it seemed to me reading your report that you were
19 comparing and contrasting specific and non-specific amplification
20 generally and not necessarily comparing and contrasting specific and
21 non-specific amplification in the context of a process where the target
22 nucleotide had already been isolated from the sample; is that right?

23 * * * *

24 THE WITNESS: I may have been. I mean, I was talking about
25 specific and non-specific amplification methods, and I was trying to
26 describe what that meant and not the entire processes that might be
27 used in.

28 (Mullis Dep., Ex. B, at 111.)⁶

Dr. Mullis's generalized analysis relies upon the analogy of searching for a needle in a
haystack. He contends that specific amplification methods increase the copies of the needle until

⁶ Dr. Mullis's expert report is substantively identical to his Declaration that accompanied Gen-Probe's motion. See Mullis Dep., Ex. B, at 17-19.

1 there are more copies of the needle than the haystack. (Mullis Decl. at ¶ 22.) But Dr. Mullis's
2 declaration does *not* address the case in which the needle is amplified after it has already been
3 separated from the haystack. Plainly, the relevance of the distinctions between absolute and relative
4 increases in the sequence of interest emphasized by Dr. Mullis is eliminated entirely when the needle
5 *is* the haystack – as is the case when the target sequence has been separated from the sample by
6 target capture. Indeed, when asked to consider the issue in the context of the claimed invention of
7 the '338 patent, Dr. Mullis admitted that isolation of the target before amplification could address
8 many of the differences he noted in his expert report and declaration. He testified "once you have
9 the thing isolated by itself, maybe the non-specific amplification will help you bring that up to a
10 level of detectability." (Mullis Dep., Ex. B, at 117.)

11 Accordingly, the Court should dismiss as irrelevant Dr. Mullis's factual assertions that
12 underlie Gen-Probe's motion because they do not address the proper analysis of infringement under
13 the doctrine of equivalents. Consequently, Gen-Probe's motion does not meet the required showing
14 that no genuine issue of material fact exists concerning the equivalence issue, and therefore Gen-
15 Probe's motion should be denied. —

16 **B. In the Context of the Invention, TMA is Equivalent to the Amplification**
17 **Techniques of the '338 Patent**

18 More importantly, when he performed the proper analysis, Dr. Mullis confirmed that TMA is
19 equivalent to the amplification techniques disclosed in the '338 patent. The equivalence is most
20 clearly shown in another document produced by Dr. Mullis, attached as Ex. F. That document
21 shows that in the context of the claimed invention, Dr. Mullis views TMA as performing the same
22 function to achieve the same result as the amplification techniques of the '338 patent. In that
23 document, Dr. Mullis wrote:

24 TMA is not quite as specific as PCR thus the need for pre-purification.

25 (Ex. F.)

26 Dr. Mullis explained that the TMA technique used by Gen-Probe "is about a million times
27 less specific" than PCR. (Mullis Dep., Ex. B, at 119.) By "pre-purification," Dr. Mullis meant a
28 target capture step, as disclosed in the '338 patent. (Mullis Dep., Ex. B, at 122.) This handwritten
note from Gen-Probe's own expert is dispositive of the equivalence issue because it shows that the

1 TMA technique as sufficiently non-specific as to require a target capture step prior to its use for the
2 very same reason that target capture is employed prior to amplification in the claims of the '338
3 patent.⁷

4 Thus, the TMA technique used in Gen-Probe's products is subject to the same limitations, *i.e.*
5 non-specificity, as the amplification techniques the Court has held are within the claims of the '338
6 patent and so performs the same function, in the same way, to achieve the same result as the
7 amplification techniques of the '338 patent. That is why Gen-Probe uses target capture in its
8 HIV/HCV assay. The '338 patent teaches that if an amplification technique is not sufficiently
9 specific, a target capture step is required to achieve appropriate sensitivity and specificity required in
10 a diagnostic assay. Gen-Probe's TMA technique is sufficiently non-specific that it benefits
11 immensely from target capture as claimed in the '338 patent. In the context of the '338 patent, the
12 amplification techniques of the patent and Gen-Probe's TMA technique are equivalent.⁸

13 Accordingly, under the correct doctrine of equivalents analysis, Dr. Mullis's testimony shows
14 that Gen-Probe's TMA process, as used in its HIV/HCV assay, is equivalent to the amplification
15 step of the claimed invention of the '338 patent. At a minimum, a genuine issue of material fact is
16 presented precluding the entry of summary judgment.

17 **C. Gen-Probe's Arguments Concerning Exponential Amplification Are Not**
18 **Relevant**

19 Finally, Dr. Mullis's deposition testimony demonstrates that the distinction Gen-Probe has
20 attempted to draw between "exponential" and "linear" amplification techniques is not relevant to the
21 doctrine of equivalents analysis. "Specific" amplification techniques are not necessarily
22 "exponential" techniques – indeed, Dr. Mullis testified that specific amplification techniques can
23 include linear amplification. (Mullis Dep., Ex. B, at 60-61, 102-03.) Moreover, to the extent Gen-

24
25 ⁷ Dr. Mullis's testimony concerning the limitations of TMA are particularly instructive given
that he *invented* the TMA process. See Mullis Dep., Ex. B, at 123-24.

26 ⁸ As previously set forth in Vysis' Opposition memorandum, specificity is a matter of degree,
27 and depends on the amplification conditions and the intrinsic properties of the amplification
28 protocol. (Persing Decl., ¶ 6.) Dr. Mullis agreed (Mullis Dep., Ex. B, at 75-77) and acknowledged
that even PCR is not totally specific. (Mullis Dep., Ex. B, at 59; see also Exs. D, G, H, I, J; Mullis
Dep., Ex. B, at 67-83.)

1 Probe suggests that linear amplification methods are not useful for a diagnostic assay (and thus do
2 not produce the same result as exponential methods), Dr. Mullis's testimony belies that point as well.
3 Dr. Mullis's own PCR patent contains a claim to a method in which only *four* copies of a target
4 nucleic acid are created from a single template. (Mullis Dep., Ex. B, at 57-58.) Dr. Mullis has
5 himself patented detection methods using this same four-fold amplification scheme. (Ex. K, claim
6 1.) Such methods could not have been patented if they did not possess practical utility. See 35
7 U.S.C. § 101; *Brenner v. Manson*, 383 U.S. 519, 528-29 (1966).

8 Contrary to Dr. Mullis's statements in his Declaration (Mullis Decl., ¶ 25), non-specific
9 amplification techniques used in accordance with the process of the '338 patent must be viewed as
10 possessing at least this same degree of utility in a diagnostic assay. If a "useful" detection assay
11 employing PCR can involve the creation of only four copies, a linear amplification technique (in
12 which four copies would be made after only four amplification cycles) must also be considered
13 useful.

14 IV. CONCLUSION

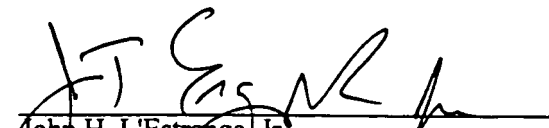
15 Dr. Mullis's testimony compels reconsideration of the Court's earlier claim construction. As
16 demonstrated by Dr. Mullis, one skilled in the art in 1987 would understand the term "amplifying" in
17 the claims of the '338 patent to encompass specific amplification techniques, such as PCR. Indeed,
18 a specific amplification technique is explicitly disclosed in the patent and the most widely used *in*
19 *vitro* amplification technique at the time was a specific technique. Further, Dr. Mullis's testimony
20 shows that when the correct analysis is performed, TMA is equivalent to the amplification
21 techniques the Court has found to be within the literal scope of the '338 claims and performs
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the same function, in the same way, to achieve the same result as the amplification step of the process claimed in the patent. Accordingly, Gen-Probe's motion should be denied.

Date: November 8, 2001

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15 SOUTHERN DISTRICT OF CALIFORNIA

16 GEN-PROBE, INCORPORATED,)
17 Plaintiff,)
18 v.)
19)
20 VYSIS, INC.,)
21 Defendant.)

CASE NO.: 99CV 2668H (AJB)

CERTIFICATE OF SERVICE

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CERTIFICATE OF SERVICE

I, the undersigned, declare under penalty of perjury that I am over the age of eighteen years and not a party to this action; my business address is 4665 Park Blvd., San Diego, California 92116; and that I served the below-named persons the following documents:

VYSIS' SUPPLEMENTAL OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

VYSIS' SUPPLEMENTAL STATEMENT OF DISPUTED FACTS IN OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

SUPPLEMENTAL DECLARATION OF L. SCOTT BURWELL IN SUPPORT OF VYSIS' SUPPLEMENTAL OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

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Executed on November 8, 2001, at San Diego, California.

DIVERSIFIED LEGAL SERVICES, INC.

